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EDITORIAL COMMENT

The Importance of Overcoming Resistance*

Norman A. Paradis, MD

Since the pioneering studies of Pearson and Redding (1), there has been a focus on arterial pressure in the development of chest compression-based cardiopulmonary resuscitation (CPR). This made sense: cardiac arrest is an absence of pump function resulting in a loss of the arterial-to-venous perfusion gradient that is the driving force for blood flow.

Once the paradigm of resuscitation research became enhancement of arterial pressure, the pathways to improving outcomes undertaken by most investigators also became concentrated: increased CPR force and pressor drugs.

The hypothesis that return of spontaneous circulation (ROSC) required therapy directed at raising arterial pressure was supported by the associations between aortic pressure and the aortic-to-right atrial pressure difference and ROSC (2). These associations, however, should not be mistaken for actual vital organ blood flow. Although an arterial-to-venous pressure gradient may be necessary for perfusion, it may not be sufficient. If, for instance, there is insurmountable resistance in the circuit between the arterial and venous systems, the arterial pressure head may be insufficient for actual blood flow.

If a simplified equation predictive of blood flow includes the aortic-to-right atrial pressure in its numerator, some measure of resistance belongs in the denominator.

This is not a new insight. Toward the end of the past millennium, it was common to talk about a "no-reflow phenomenon" as a centrally important etiology in post-anoxic encephalopathy. Peter Safar advocated a brief period of hypertension just after ROSC to try to push through the resistance and reestablish blood flow to the brain.

From the beginning of modern resuscitation research, there has always been an opportunity to improve vital organ blood flow during CPR not only by enhancement of arterial pressure but by lowering resistance. And it is basic physiology that the two big resistors in the circulatory circuit are the systemic and pulmonary vascular beds. They are just sitting there as potential pharmacological or mechanical targets. Lower the resistance, raise the flow.

Although it has not been proven that the global ischemia of cardiac arrest is associated with vital organ vasoconstriction during CPR, it is a reasonable hypothesis. So theoretically, one could administer vasodilators to lower vascular resistance and improve vital organ blood flow. But there is an obvious problem with this approach: the same vasodilator that may open pre-capillary sphincters and improve tissue blood flow will also cause arterial hypotension and a loss of the driving pressure gradient.

And "there's the rub."

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Ripeckyj et al. (3), of the "Minneapolis group," in this issue of *JACC: Basic to Translational Science* may be the first to attempt a therapeutic intervention directed at lowering the resistance to blood flow pharmacologically (4). They chose sodium

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From Emergency Medicine, Geisel School of Medicine at Dartmouth, Dartmouth College, Lebanon, New Hampshire. Dr. Paradis is a consultant for ZOLL Medical; is a founder of CPR Therapeutics; and has patents and patent applications relating to CPR devices.

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nitroprusside (SNP), which is both a venous and an arterial vasodilator. As pointed out by Jim Niemann (5), it would be hard to overstate the innovation (and courage) in their approach. The administration of vasodilators during CPR runs counter to the conventional thinking that has made drugs such as epinephrine first-line agents after failure of defibrillation and basic life support. It would have been reasonable to predict that SNP would lower perfusion pressure, organ blood flow, and ROSC.

These investigators addressed the potential loss of arterial pressure by the combination of SNP with mechanical adjuncts to CPR (6). These included improving venous return through active decompression and an impedance threshold device, as well as abdominal binding to enhance arterial-side CPR pump afterload. It is worth noting that some of these same investigators were involved in the development of two of these innovations as well. It can be argued that they are the most innovative group active in resuscitation research.

In a series of porcine studies, Yannopoulos et al. (6) demonstrated that application of SNP-enhanced CPR (SNPeCPR) is associated with improved rates of ROSC and indicators of hemodynamic status and neurological outcome. Of particular note, SNPeCPR reportedly can achieve ROSC after laboratory "down times" from which animals cannot normally be reliably resuscitated.

In this issue, these investigators extend this work by demonstrating that SNPeCPR may be associated with relative arterial hypoxemia (3). This was not unexpected, as it is a reasonable conjecture that SNP-induced pulmonary vasodilation would be associated with increased pulmonary shunt.

Reassuringly, the investigators found that the administration of supplemental oxygen corrects arterial hypoxemia and that the combination of SNPeCPRs improved hemodynamics and supplemental oxygen appears to result in improved oxygen delivery: the bottom line in CPR.

To say that there has been resistance to SNPeCPR itself might be an understatement. Eight years after the original publication, all work on SNPeCPR continues to come from this one laboratory. Correcting this situation should be a high priority in resuscitation research. Before human clinical trials can be undertaken, work on SNPeCPR needs to be replicated, and if possible extended, in other laboratories.

A number of basic physiological and pharmacological questions remain. 1) What are the relative contributions of systemic versus pulmonary vasodilation to the efficacy of this approach? Is most of the benefit from vasodilation in the cardiac and cerebral circulations or does it accrue secondary to overall improved blood flow through the pulmonary bed? 2) Is SNP the ideal pharmacological agent? The list of alternative agents is, unfortunately, relatively long. It would include other nitrates, calcium-channel blockers, methylxanthines, and others. 3) Would selective systemic versus pulmonary vasodilators be more effective? If pulmonary vasodilation is selectively effective, ventilation with nitric oxide or administration of phosphodiesterase inhibitors should be considered. 4) Were these CPR adjuncts necessary to offset the loss of arterial perfusion pressure? There were two variables here right from the beginning: the mechanisms of CPR and the pharmacology of the vasodilator. What are the odds that the Minneapolis group got the optimal combination right out of the box?

There will always be a need for initial basic life support by first responders in the treatment of out-of-hospital sudden death. Even in systems with resuscitation centers built around emergency cardiopulmonary bypass, there will still be a need for optimized advanced cardiac life support en route to the hospital. SNPeCPR currently appears "best in breed" among the enhancements to advanced cardiac life support. Yannopoulos and colleagues should be applauded for the innovation they conceived and their persistence in continuing its development (3,6).

The rest of the resuscitation research community needs to support these efforts through replication and extension of SNPeCPR research. Sudden cardiac death remains among the leading single causes of lost years of life in Western countries. Improvements in outcomes will require actual innovation, beyond what can be achieved solely from more widespread application of classic CPR.

ADDRESS FOR CORRESPONDENCE: Dr. Norman A. Paradis, Geisel School of Medicine at Dartmouth, Emergency Medicine, Dartmouth College, One Medical Center Drive, Lebanon, New Hampshire 03756. E-mail: Norman.A.Paradis@hitchcock.org.

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